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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,715	11/07/2001	Brent W. Weston	5470-259CT	8629

20792 7590 10/18/2004

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,715	WESTON ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-11,16-18 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-11,16-18 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed July 23, 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed March 25, 2004 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement filed July 23, 2004 fails to comply with 37 CFR 1.97(c) because it lacks the fee set forth in 37 CFR 1.17(p). It has been placed in the application file, but the information referred to therein has not been considered.

Priority

The first line of the specification recites "This application is a continuation of co-pending United States Application Serial No. 09/556,031, filed on April 20, 2000 (now allowed) which claims priority to U.S. Provisional Application Serial No. 60/131,068, filed April 26, 1999. However, 09/556,031 has matured into U. S. Patent Number 6,350,868. In the absence of an application data sheet, the first line of the specification should be amended to include a reference to the patent number of the previously allowed parent.

Response to Arguments, 35 U.S.C. § 112 first paragraph enablement

Claims 9-11, 16-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of Fucosyltransferase 3 and 6 (FUT3 AND FUT6 respectively) expression *in vitro*, does not reasonably provide enablement for cancer treatment via antisense-mediated inhibition of FUT3 and FUT6 expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argue that the application of the instantly claimed method of treating cancer requires routine effort, and not undue experimentation, and is therefore enabled. In support Applicants have submitted several articles that allegedly support Applicant's contention that antisense nucleotides have been shown to treat cancer. Applicants conclude that based upon the information provided in these articles, that one of skill could use the sequences and fragments claimed to achieve cancer treatment.

These arguments are not considered convincing. As a first matter, only one of five articles cited by Applicants were published on or before applicants filing date. As per M.P.E.P. 2164.05(a) [R-2], the specification must be enabling as of the filing date. On its face, this submission of articles published after the instant filing date thus cannot be considered to support claims to treating cancer. However, they are addressed below.

Umberto Galderisi et al. is alleged to disclose the use of "oligonucleotides" (Fomiversin) as selective inhibitors of gene expression, which have been FDA approved for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Applicants argue therefore that antisense

technology has been successfully employed in the treatment of a disease state. It is pointed out that Fomiversin is only one oligonucleotide. Furthermore, Umberto-Galderisi indicates that "The use of antisense molecules to modify gene expression is variable in its efficacy and reliability, raising objections about their use a therapeutic agents." (See Abstract). It is also noted that today in late 2004, Fomiversin is still the only drug approved by the FDA, and that none of the other drugs referenced by Umberto-Galderisi have received such approval.

Regarding Fomiversin, attached is a Reuter's article on a recent clinical trial failure (results announced March 17, 2003), wherein it is stated that "Isis currently makes the world's only commercial antisense drug--a treatment for a rare types of eye infection in AIDS patients. Many once promising antisense drugs have failed, including experimental therapies from Isis for HIV and genital warts" (this article is included to rebut applicants' arguments and does not constitute a new grounds of rejection). Moreover, fomiversin is not representative of any antisense-based cancer treatment as encompassed in applicants' claims, because fomiversin only treats a rare disease and is injected directly into the eye. This drug thus achieves high local concentrations that help circumnavigate the problematic issue of crossing cell membranes in high enough quantity to attain gene inhibition. Applicants claims by contrast broadly seek to treat any cancer with the instant oligos; presumably, most somatic diseases would not be as vulnerable to antisense administration as the eye is with fomiversin, rendering applicants' instant comparison with fomiversin of little relevance to the enablement of claims broadly seeking to treat any disease associated with overproduction of FUT3 or FUT6.

Applicants have cited papers by Burkhart et al., Geary et al., Smith et al., and Rudin et al. that show antisense activity taking place *in vivo*. While only Smith was published before

applicants priority date and thus may be properly considered in assessing the state of the prior art, it is agreed that these articles indeed demonstrate *in vivo* success using antisense oligos to their respective targets. It has never been argued that the prior art is devoid of reports describing the successful use of antisense oligonucleotides to inhibit the expression of a gene *in vivo*. However, this is not the test for enablement; the test is whether undue experimentation is required to practice the claimed invention, wherein such an assessment is made only when considering the specification and prior art as a whole. It is maintained that these results are considered to be irregular and unpredictable when viewed against the state of the art as a whole, as evidenced by the numerous review articles and citations therefrom in this action and the previous action mailed March 25, 2004.

For example, in further support of the numerous reviews citing unpredictability in previous Office actions, more recent publications indicate that progress in using antisense to achieve *in vivo* gene inhibition has been grudgingly slow. For example, a recent scientific review of the state of the art of nucleic acid therapeutics has been written by Opalinska and Gewirtz (Nature Reviews, 2002. 1:503-514) indicating that "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain...It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field." (page 503, 2nd paragraph). They conclude that "...it is widely appreciated that the ability of nucleic acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability." Thus, this manuscript published four years after applicant's effective filing date, when combined with the five previously cited review articles

indicating similar unpredictability, reinforces the view that the field as a whole remains unpredictable.

Furthermore, Branch in 1998 (the year of applicants instant filing date, of record) indicated that Krieg, a prominent scientist in the field, expressed doubts about such published reports of antisense efficacy, stating that "the estimate that many people have given me of the percentage of accurate published antisense papers ranges from 50% of them being accurate to 5% being accurate". Thus, it is maintained that the state of the art of using oligonucleotides to achieve clinical treatment is highly unpredictable.

Applicants also argue that the instant disclosure reports that cell cultures into which the entire FUT3 antisense transcript had been transfected were unable to colonize the liver when they were injected into the spleens of nude mice. Applicants argue that these results provide target validation for inhibition of carcinoma metastasis with antisense FUT sequences.

However, this argument glides over the fact that the cells injected *in vivo* in this study had been previously transfected with the full length antisense sequence, while the cells were still in culture. Thus, the art recognized barrier of getting enough of the antisense oligo into the cell, which is the single most difficult and art recognized obstacle in achieving *in vivo* gene inhibition, has been completely circumvented by such an approach. Furthermore, this method is not reflective of the methods claimed by applicants, which seek to inject oligos intravenously, wherein the oligos must still traverse the cell membrane in sufficient quantities to achieve inhibition. Secondly, the exemplified approach uses the full-length antisense transcript rather than the individual oligonucleotide sequences that are claimed instantly in methods of achieving cancer treatment. It is not clear how the exemplified approach enables the claimed method, since

the exemplified method uses cells previously treated with a different compound (i.e. the full length antisense) than the compounds claimed for use in the instant methods.

For these reasons, the method of treating cancer comprising administering antisense oligos are considered to require undue trial and error experimentation with no reasonable assurance that any success would be forthcoming. Accordingly, the invention of the above claims is not considered to be enabled.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JD Schultz, PhD

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